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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/511,776 02/24/00 CRAIG

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HM12/0607

EXAMINER

GARET, G	
ART UNIT	PAPER NUMBER

1641
DATE MAILED:

7
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

09/511,776

Applicant(s)

CRAIG ET AL.

Examiner

Gailene R. Gabel

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 February 2000.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-22 is/are pending in the application.
- 4a) Of the above claim(s) 15-18 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-14 and 19-22 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☒ Claims 1-22 are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- 15) ☒ Notice of References Cited (PTO-892)
- 16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
- 18) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 19) ☐ Notice of Informal Patent Application (PTO-152)
- 20) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, claims 1-14 and 19-22, with traverse, filed 3/13/01 in Paper No. 5 is acknowledged and has been entered. Claims 15-18 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being claims drawn to a non-elected invention. Accordingly, claims 1-14 and 19-22 are under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-14 and 20-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite in reciting "capable of" because it fails to recite a positive and active method step. See also claims 2 and 3.

Claim 1 is incomplete for omitting essential elements and/or essential structural cooperative relationships of elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted element is a label which provides for effecting the generation of a signal upon binding of the first binding partner and the protein. Specifically, step b) implies, rather than specifically defines, that the first binding partner has a label conjugated thereto.

Claim 1 is vague and indefinite in reciting "detecting labeling of the protein by the first binding partner", first and second occurrences because as recited, it appears that the protein has a label conjugated thereto wherein signal generation is effected by the binding of an "unlabeled" first binding partner to the "labeled" protein", which is not what Applicants intend based on subsequent dependent claims.

Claim 5 is vague and indefinite in reciting "the protein is isolated by binding to said capture ligand" because it is unclear what is encompassed by the term "isolated" in relation to the "capture ligand". For example, do Applicants intend to capture/immobilize/separate the protein for detection.

Claims 4 and 6 use inconsistent language in reciting "solid phase substrate" and "solid phase support". Alternatively, it is unclear how the "solid phase support" in claim 5 is differentially distinct from in relation to the "solid phase substrate" in claim 3. See also claim 12.

Regarding claim 7, "and/or" renders the claim indefinite because the claim includes elements not actually disclosed (those encompassed by "and/or"), thereby rendering the scope of the claim unascertainable. See MPEP § 2173.05(d). See also claim 22.

Regarding claim 7, the term "other" renders the claim indefinite because the claim includes elements not actually disclosed (those encompassed by "other"), thereby rendering the scope of the claim unascertainable. See MPEP § 2173.05(d).

Claim 7 recites improper and overlapping Markush groups in reciting "selected from the group consisting of a fluorescent or other luminescent label, a domain of an

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enzyme, a radiolabel, a chemical or enzymatic label and a heavy metal or other radioopaque label".

Claim 10 is indefinite in reciting "FRET". Acronyms and abbreviations must be recited at least one time in a given set of claims.

Claim 13 is vague and indefinite in reciting "unbound labeled binding partner" first and second occurrence, because it is unclear which antecedent "binding partner" is being referred to.

Claim 14 is indefinite in reciting "FCS". Acronyms and abbreviations must be recited at least one time in a given set of claims.

Double Patenting

3. Claims 1, 3-14, and 19-22 of this application conflict with claims 1-13 and 18-21 of Application No. 09/258,452. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

4. Claims 1, 3-14 and 19-22 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-13 and 18-21 of copending Application No. 09/258,452. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

5. Claims 1, 3-9, and 12-13 are rejected under 35 U.S.C. 102(e) as being anticipated by Prusiner et al. (US 5,891,641).

Prusiner et al. disclose a method for determining a diseased related conformational state of a protein such as PrP^{Sc} in a sample (see column 5, lines 21-58). Prusiner et al. specifically disclose contacting the protein with a labeled antibody that binds (has a higher binding affinity) to the protein in a manner dependent on the conformational state of the protein; i.e. PrP^C (native or non-disease state) or PrP^{Sc} (diseased conformation) (see column 4, lines 24-56, column 12, lines 4-28, and column 17, lines 49-58). The antibody is detectably labeled with fluorophores, radioisotopes,

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enzymes, etc. so as to detect labeling of the protein wherein a generation of signal is indicative of the conformational state of the protein (see column 12, lines 64-67).

Prusiner et al. also disclose contacting the protein with a second antibody or capture ligand to immobilize the protein on a solid phase substrate (see column 4, lines 5-10).

Prusiner et al. also disclose that recombinant prion proteins can be covalently linked (chemically crosslinked) to a solid phase substrate (polystyrene plates) (see column 6, lines 1-3). Standard preparations of disease related conformational state proteins such as prion proteins are produced for use in calibration and validation testing of the diagnostic sensitivity, specificity and predictive values of the assay (see column 22, lines 58-61). Antibody binding to the disease related conformation is measured using time resolved, dissociation enhanced fluorescence (see column 17, lines 62-65).

6. Claims 1, 3-9, and 12-13 are rejected under 35 U.S.C. 102(e) as being anticipated by Martinez et al. (WO 98/41872).

Martinez et al. disclose a method for determining a conformational state of a protein (activated versus inactivated) such as a cytokine receptor or growth hormone receptor (GHR) in a sample. Martinez et al. specifically disclose contacting the protein with an antibody (GHR05) that selectively binds to the protein in a manner dependent on its conformational state, thereby forming a complex (see Abstract and page 1, lines 16-21). Martinez et al. disclose contacting the protein with a second antibody or capture ligand to immobilize the protein on a solid phase substrate in a sandwich capture assay (see page 7, lines 26-30). Alternatively, the protein can be covalently

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linked to avidin-coated solid phase substrate (microtiter plate) to capture the antibody in an antibody capture assay (see page 7, lines 10-19). The mAb GHR05 is detectably labeled with enzyme so as to detect labeling of the protein wherein a generation of signal is indicative of the conformational state of the protein (see page 12, lines 23-31).

7. Claims 1, 3, and 7-11 are rejected under 35 U.S.C. 102(e) as being anticipated by Tsien et al. (US 5,998,204).

Tsien et al. disclose fluorescent indicators and methods for using them to determine concentration of binding partners (analyte) by determining a change in the conformational state of a binding protein (see column 4, lines 48-57). Specifically, Tsien et al. disclose the fluorescence indicators comprising a protein (binding protein) that changes conformation upon binding a first binding partner, wherein a first label (donor fluorescent moiety) is covalently bound to a binding protein moiety and a second label (acceptor fluorescent moiety) is bound to a binding protein moiety so that when the binding protein binds a binding partner, the fluorescent indicator is caused to change in conformation (see column 1, lines 48-64). Specifically, the donor and acceptor fluorescent moieties are bound to a binding protein moiety that changes conformation upon binding the analyte. Tsien et al. disclose that the donor moiety and the acceptor moiety change position relative to each other upon binding, thus altering fluorescence resonance energy transfer between the donor and acceptor moiety for purpose of measurement (see column 6, lines 38-60).

8. Claims 2-3, 5-9, and 11 are rejected under 35 U.S.C. 102(e) as being anticipated by Eberwine et al. (WO 96/05847).

Eberwine et al. disclose measuring activity of an enzyme wherein the conformation of a protein is dependent upon the post-translational modification activity of the enzyme. The post-translational modification activities include phosphorylation and glycosylation occurring on the proteins. Eberwine et al. disclose contacting the protein which has a site (epitope) for post-translational modification with the enzyme. Eberwine et al. further disclose adding antibodies to bind at least two epitopes on the protein wherein one of the antibodies binds the protein in a manner dependent upon or specific for the post-translational modification of the protein by the enzyme. For detection, the antibodies are first modified by binding, thereto, a first and a second nucleotide sequence. Upon binding the modified antibodies with the protein, complementary base pair sequences on the antibodies eventually form a stable double stranded duplex which upon treatment with restriction enzymes, digestion products are produced for detection of post-translation modification activity on the protein (see page 4, lines 10-34 and page 11, lines 3-33). The nucleotide sequences used to modify the antibodies can be incorporated into solid phase (see column 6, lines 33-35).

9. Claims 2-14 are rejected under 35 U.S.C. 102(e) as being anticipated by Epps et al. (US 6,203,994).

Epps et al. disclose measuring activity of an enzyme wherein the conformation of a protein is dependent upon the post-translational modification activity of the enzyme.

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The post-translational modification activities include phosphorylation and dephosphorylation activity of a kinase or phosphatase (see Abstract). Epps et al. disclose contacting the enzyme with a protein (amino acid) that is capable of being phosphorylated by the enzyme and a reporter molecule comprising a fluorescent label and a phosphorylated protein, and an antibody that selectively binds to the phosphorylated protein (see column 2, lines 33-54 and column 4, lines 20-41). Epps et al. disclose that the antibody binds the protein in a manner dependent upon the post-translational modification by the enzyme. Epps et al. specifically disclose measuring activity of the enzyme using either fluorescence correlation spectroscopy (FCS) or fluorescence resonance energy transfer (FRET) (see columns 2-7).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

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consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 10-11 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Prusiner et al. (US 5,891,641) or Martinez et al. (WO 98/41872) or Eberwine et al. (WO 96/05847) in view of Epps et al. (US 6,203,994) or Kinjo et al. (Nucleic Acids Research, 1995).

Prusiner et al., Martinez et al., and Eberwine et al. have been discussed supra. Prusiner et al., Martinez et al., and Eberwine et al. differ in failing to use fluorescence resonance energy transfer (FRET) or fluorescence correlation spectroscopy (FCS) to measure binding between proteins and binding partners.

Epps et al. has been discussed supra.

Kinjo et al. teach using fluorescence correlation spectroscopy (FCS) in monitoring conformational state (translational diffusion) of a protein. Specifically, Kinjo et al. teach that interaction kinetics of a fluorescent ligand with a target can be measured by correlation function which describes the translational diffusion of bound and free ligand.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to have substituted another known applicable detection assay such as FCS taught by Kinjo or FCS and FRET taught by Epps into the method of Prusiner, Martinez, or Eberwine because Kinjo and Epps specifically taught that FCS and FRET are capable of functionally monitoring ligand interaction kinetics, conformational state and/or post-translational modification of proteins by enzyme; thereby constituting an

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obvious design choice of a detection system in the methods of Prusiner, Martinez, and Eberwine.

11. Claims 19-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Prusiner et al. (US 5,891,641) or Martinez et al. (WO 98/41872) or Eberwine et al. (WO 96/05847) or Epps et al. (US 6,203,994) or Tsien et al. (US 5,998,204) in view of Foster et al. (US 4,444,879).

Prusiner et al., Martinez et al., Tsien et al., Eberwine et al., and Epps et al. differ in failing to incorporate the protein standards, binding partners, and packaging components into a kit format.

Foster et al. teaches kit components with instructions for use in assay methods.

It would have been obvious to have incorporated the protein standards, binding partners and label reagents taught by Prusiner, Martinez, Tsien, Eberwine, and Epps into a kit format for use in a method of determining the conformational state of a protein because kit formats are recognized for their advantage in convenience and economy.

12. No claims are allowed.

Remarks

13. Prior art made of record are not relied upon but considered pertinent to the applicants' disclosure:

Prusiner et al. (WO 98/37411) disclose a method for determining a diseased related conformational state of a protein such as PrP^{Sc} in a sample using antibodies with high affinity thereto.

Becker et al. (EP 0 613 007 A2) disclose antibodies having specificity for a β amyloid peptide which is predominantly in a β sheet conformation state.

Pakula et al. (EP 0 770 876 A1) disclose ligands that bind a target protein in its native conformation or in its unfolded conformation.

Ha et al. (Proc. Natl. Acad. Sci., 1999) teach FRET and FCS to analyze distinct patterns attributed to protein conformational dynamics.

Lillo et al. (Biochemistry, 1997) teach using FRET in protein folding studies.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (703) 305-0807. The examiner can normally be reached on Monday to Thursday, 6:30 AM - 4:00 PM and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (703) 308-3399. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

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grg
May 26, 2001



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